[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Tertiary Arsines and Arsine Oxides. II[1]

BY F. F. BLICKE AND S. R. SAFIR[2]

During our studies of arsonium compounds we have prepared a number of arsines and arsine oxides as follows.

4 - Bromophenyldibromoarsine.—4 - Bromophenylarsonic acid,[3] 50 g., suspended in 200 cc. of hydrobromic acid (sp. gr. 1.55) which contained a few drops of hydriodic acid, was treated with a stream of sulfur dioxide, the precipitated, oily arsine separated and dried with calcium chloride; b. p. 180–185° at 12 mm.; yield 60 g. (86%).

Anal. Calcd. for $C_6H_4AsBr_3$: As, 19.17; Br, 61.36. Found: As, 19.11; Br, 61.12.

Dimethyl - 4 - bromophenylarsine.—4 - Bromophenyldibromoarsine, 60 g., was added, dropwise, to methylmagnesium iodide prepared from 29 cc. of methyl iodide, 11.3 g. of magnesium and 300 cc. of ether. After several hours the mixture was treated with ice and dilute hydrochloric acid, the ether layer shaken with 20% sodium hydroxide solution and then dried over stick sodium hydroxide. The arsine boiled at 120–125°[4] under 11 mm.; yield 33 g. (83%).

Anal. Calcd. for $C_8H_{10}AsBr$: As, 28.70; Br, 30.62. Found: As, 28.76; Br, 30.85.

Di-(3-nitro-4-hydroxyphenyl)-iodoarsine.—A solution of 1.2 g. of sodium iodide in 15 cc. of acetone was added to 1.0 g. of di-(3-nitro-4-hydroxyphenyl)-chloroarsine[5] dissolved in an equal volume of acetone. After twelve hours the mixture was filtered and the solvent removed. The yellow gum crystallized when triturated with a little water; m. p. 126–128° after recrystallization from acetic acid; yield 1 g.

Anal. Calcd. for $C_{12}H_8O_6N_2AsI$: As, 15.67; I, 26.55. Found: As, 15.61; I, 26.63.

Methyldi-(4-bromophenyl)-arsine.—A mixture of 29 g. of 1,4-dibromobenzene, 3.0 g. of magnesium, a crystal of iodine and 200 cc. of ether was heated until the reaction began and then cooled with ice until practically all of the magnesium had disappeared. The Grignard reagent was stirred and 23 g. of methyl-4-bromophenyliodoarsine[6] added in portions. After one hour the mixture was treated with ice and hydrochloric acid, the ether layer shaken with 20% sodium hydroxide solution and dried over stick sodium hydroxide; b. p. 230–240° at 14 mm.; yield 19.5 g. (79%); m. p. 71–73°.

Anal. Calcd. for $C_{13}H_{11}AsBr_2$: As, 18.64; Br, 39.77. Found: As, 18.71; Br, 39.84.

Methyldi-(3-nitro-4-bromophenyl)-arsine.—A solution of 5.0 g. of methyldi-(3-nitro-4-bromophenyl)-arsine oxide (described below), 4.0 g. of 50% hypophosphorous acid, one drop of hydriodic acid and 20 cc. of acetic acid was heated for four hours on a steam-bath, cooled and the acetic acid layer decanted from the oily product. The latter became granular after it had been triturated with about 10 cc. of water. An additional small quantity of crystalline arsine was obtained by dilution of the acetic acid layer with water; yield 4.1 g. (86%); m. p. 82–84° after recrystallization from absolute alcohol.

Anal. Calcd. for $C_{13}H_9O_4N_2AsBr$: As, 15.23; Br, 32.48. Found: As, 15.38; Br, 32.58.

Tri - (4 - bromophenyl) - arsine.—4 - Bromophenylmagnesium bromide, prepared from 94.4 g. of 1,4-dibromobenzene, 9.7 g. of magnesium and 400 cc. of ether, was stirred and 39.1 g. of 4-bromophenyldibromoarsine added in portions. The mixture was stirred for one hour, decomposed with ice and hydrochloric acid, the ether layer shaken with 20% sodium hydroxide solution and dried over sodium hydroxide; b. p. 285–290° at 7 mm.; yield 37 g. (68%); m. p. 132–134° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{18}H_{12}AsBr_3$: As, 13.80; Br, 44.18. Found: As, 13.86; Br, 44.02.

Tri-(3-nitro-4-bromophenyl)-arsine.—A mixture of 3.4 g. of tri-(3-nitro-4-bromophenyl)-arsine oxide (described below), 3.0 cc. of 50% hypophosphorous acid, one drop of hydriodic acid and 20 cc. of acetic acid was heated for four hours on a steam-bath, the colorless precipitate filtered and recrystallized from acetic acid; yield 2.8 g. (87%); m. p. 189–191° decompn.

Anal. Calcd. for $C_{18}H_9O_6N_3AsBr_3$: As, 11.05; Br, 35.38. Found: As, 10.96; Br, 35.45.

Methyldi-(4-bromophenyl)-arsine Oxide.—One gram of the required arsine, dissolved in 30 cc. of acetone, was stirred with 0.36 g. of powdered potassium permanganate for one-half hour, the mixture decolorized with a few drops of isopropyl alcohol, filtered and the filtrate evaporated to dryness. The oxide was recrystallized from benzene; yield 1.0 g. (96%); m. p. 221–223°.

Anal. Calcd. for $C_{13}H_{11}OAsBr_2$: As, 17.93; Br, 38.25. Found: As, 17.95; Br, 38.10.

Methyldi-(3-nitro-4-bromophenyl)-arsine Oxide.—Four grams of methyldi-(4-bromophenyl)-arsine oxide was added, in portions, to a cold mixture of 2.4 cc. of nitric acid (sp. gr. 1.60) and 5.6 cc. of concd. sulfuric acid. The clear yellow solution was heated for one-half hour on a steam-bath, cooled and poured into ice water. The precipitated yellow gum became crystalline after it had been triturated with benzene. The product was dissolved in acetone, the solution heated to the boiling point, water added until the solution showed a very slight turbidity, charcoal added and the mixture filtered. The oxide separated in crystalline form. The treatment with acetone

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[1] This paper represents part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by S. R. Safir in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

[2] Parke, Davis and Company Fellow.

[3] Blicke and Webster, THIS JOURNAL, **59**, 535 (1937).

[4] Prepared by a different method. Jones and associates (*J. Chem. Soc.*, 2287 (1932)) found 134-136° at 9 mm.

[5] Blicke, Oneto and Webster, THIS JOURNAL, **59**, 925 (1937).

[6] Prepared from 4-bromophenyldibromoarsine by the method of Hunt and Turner (*J. Chem. Soc.*, **127**, 2670 (1925)).

was repeated twice; yield practically quantitative; m. p. 213–215° decompn.

Anal. Calcd. for $C_{13}H_9O_5N_2AsBr_2$: As, 14.75; Br, 31.46. Found: As, 14.83; Br, 31.30.

Methyldi-(3-nitro-4-hydroxyphenyl)-arsine Oxide.—A suspension of 4.0 g. of methyldi-(3-nitro-4-bromophenyl)-arsine oxide in 600 cc. of water, which contained 4.0 g. of potassium hydroxide, was boiled for one hour, a solution of 10 g. of potassium hydroxide in 20 cc. of water added, the clear orange solution boiled two hours longer, concentrated on a steam-bath to a volume of 250 cc., cooled and neutralized with sulfuric acid (1:1). The pale yellow, crystalline precipitate was recrystallized from 40% acetic acid; yield 2.9 g.; m. p. 239–240° decompn.

Anal. Calcd. for $C_{13}H_{11}O_7N_2As$: As, 19.60. Found: As, 19.50.

Tri-(4-bromophenyl)-arsine Oxide.—A solution of 1.6 g. of tri-(4-bromophenyl)-arsine in 75 cc. of acetone was oxidized with 0.4 g. of potassium permanganate in the manner described above. The crude oxide was dissolved in benzene and petroleum ether (30–40°) added; the oxide separated slowly in the form of colorless needles; yield 1.3 g. (79%); m. p. 190–193°.

Anal. Calcd. for $C_{18}H_{12}OAsBr_3$: As, 13.41; Br, 42.91. Found: As, 13.44; Br, 42.70.

Tri-(3-nitro-4-bromophenyl)-arsine Oxide.—One gram of finely powdered tri-(4-bromophenyl)-arsine oxide was added, in portions, to a mixture of 0.6 cc. of nitric acid (sp. gr. 1.60) and 1.5 cc. of concd. sulfuric acid. The material was heated for two hours on a steam-bath, poured into ice water, the precipitated yellow oxide heated with 75 cc. of acetone and the mixture filtered; the treatment of the filtrate is described below. The colorless, undissolved portion (0.5 g.) was dissolved in 500 cc. of acetone and an equal volume of water added; the oxide separated in the form of colorless, glistening crystals; m. p. 252–254° decompn.

An equal volume of water was added to the yellow, acetone filtrate; 0.5 g. of yellow, sparkling crystals precipitated. The material was dissolved in the smallest possible amount of hot acetone and water added to effect precipitation; the process was repeated until the oxide was obtained in colorless form; this portion of the oxide also melted at 252–254° decompn.

Anal. Calcd. for $C_{18}H_9O_7N_3AsBr_3$: As, 10.80; Br, 34.56. Found: As, 10.87; Br, 34.37.

Summary

A number of new arsines and arsine oxides have been described.

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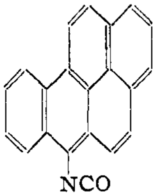
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Isocyanates of 3,4-Benzpyrene and 10-Methyl-1,2-benzanthracene

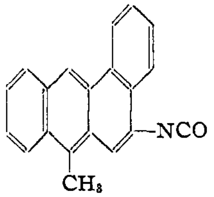
BY HUGH J. CREECH

In a continuation of a program of research on the conjugation of carcinogenic hydrocarbons with proteins[1,2] and amino acids[3], 3,4-benzpyrenyl-5-isocyanate (I) and 10-methyl-1,2-benzanthryl-3-isocyanate (II) have been synthesized.

I



II



The recent observation[4] of the pronounced carcinogenic activity of 1,2,5,6-dibenzanthryl-9-isocyanate[5] makes the tests on the present compounds of considerable significance. The 3- and 10-isocyanates[3] of 1,2-benzanthracene and their amino acid conjugates[3] have displayed no outstanding tumor-producing properties to date. The latter isocyanates are derivatives of the inactive hydrocarbon 1,2-benzanthracene, whereas the dibenzanthryl isocyanate is derived from an active parent hydrocarbon and a slightly active amine. The isocyanates described in this article are derivatives of very active hydrocarbons and thus also may be capable of causing tumors rapidly. Since it has been demonstrated[2] that isocyanates couple readily with proteins "*in vitro*,"

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(1) Creech and Franks, *Am. J. Cancer*, **30**, 555 (1937).

(2) Creech and Jones, THIS JOURNAL, **62**, 1970 (1940).

(3) Fieser and Creech, *ibid.*, **61**, 3502 (1939).

(4) I am indebted to Drs. Shields Warren and Charles E. Dunlap of the Huntington Memorial Hospital for permission to quote the following results. The subcutaneous injection of 2 mg. of 1,2,5,6-dibenzanthryl-9-isocyanate, m. p. 179–179.5° cor., dissolved in 0.2 cc. of tricaprylin produced tumors at the site of injection in all of the fourteen C_3H mice under test within 125 days, the earliest tumors being observed at 92 days. The average latent period was 111 days and the carcinogenic index was 90. It is noteworthy that this compound appears to be somewhat more active than the parent hydrocarbon [Fieser, *Am. J. Cancer*, **34**, 37 (1938); Shimkin and Andervont, *J. Natl. Cancer Inst.*, **1**, 57 (1940)]. In earlier tests [Franks and Creech, *Am. J. Cancer*, **35**, 203 (1939)] which were rendered indecisive by animal mortality due to other causes, an aqueous suspension of the dibenzanthryl isocyanate (2 mg.) produced one tumor at 159 days in an effective total of four stock white mice; the remaining three mice had not developed tumors at one year. The present observation offers one explanation of the erratic carcinogenic action of some of the dibenzanthrylcarbamido casein preparations which were known to contain adsorbed isocyanate but it does not necessarily invalidate the observations of the activity of the amino acid conjugate.[1,5]

(5) Creech and Franks, THIS JOURNAL, **60**, 127 (1938).